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# Lithium for long-term treatment of unipolar depression

Lithium is the third element in the periodic table, and although lithium is present in the natural environment and is used to make batteries, it is perhaps best known as a therapeutic drug. Lithium in various forms was used to treat neuropsychiatric disorders before falling into disuse because of concerns over toxicity. The Australian psychiatrist John Cade rediscovered lithium for the treatment of mania in 1949 and the Danish psychiatrist Mogens Schou did one of the first randomised controlled trials in mania in 1954 assessing lithium use, also suggesting the potential for use of lithium as a prophylactic drug for depressive illness. The use of lithium was opposed in the 1960s by some researchers from the Maudsley Hospital,<sup>1</sup> although evidence from later clinical trials did not support this position. Lithium is now accepted as a treatment for bipolar disorder in evidence-based guidelines, and systematic reviews show the adverse effects to be acceptable, albeit with a continuing concern about the effects of long-term use on renal function.<sup>2</sup> Despite the increasing evidence of benefits, lithium seems to be being used less. Other benefits of lithium treatment have been described, including a reduction of mortality and suicide by more than 60% in people with major depression or bipolar disorder,<sup>3</sup> a putative preventative effect for dementia,<sup>4</sup> and, perhaps most notably, a report published in 2016 showed that lithium is associated with a reduced overall cancer risk in patients with bipolar disorder, and a dose–response relationship for cancer risk reduction was observed.<sup>5</sup>

Evidence from early meta-analyses supported Schou's suggestion of the use of lithium for depression. Indeed, Souza and Goodwin<sup>6</sup> stated in 1991 that "There is no reason to doubt the efficacy of lithium in the prophylaxis of unipolar depressive illness". Recent treatment guidelines from 2017 also acknowledge the role of lithium in treating unipolar depressive disorder, although the emphasis for both acute and continuation phase treatment is on lithium as an augmenting drug (i.e., an adjunct).<sup>7</sup> The paper by Jari Tiihonen and colleagues is a most helpful addition to the available literature; they studied the risk of readmission to hospital between 1996 and 2012 in all patients in Finland (n=123 712; mean follow-up time 7.9 years) who had been admitted to hospital for unipolar depression, using nationwide databases for hospital admissions, mortality, and dispensed medications. These data show that lithium use was associated with a markedly lower risk of readmission to hospital compared with no use, whereas antidepressants and antipsychotics were not associated with any such benefits. Particularly important was the finding that risk of readmission to hospital was lower during sole lithium therapy than during its concomitant use with antidepressants. The only other drug treatments approaching the effectiveness of lithium were clozapine and amitriptyline. When analyses controlling for various biases were done, all drugs performed somewhat better; however, the same rank order in comparative effectiveness as the primary analysis was preserved. Although clearly not derived from a randomised design, these findings also broadly agree with a recent Cochrane meta-analysis of relevant trials and thus reconcile randomised and population-based data.<sup>8</sup> Tiihonen and colleagues conclude that "lithium, especially without concomitant antidepressant use, is the pharmacological treatment associated with the lowest risk of hospital readmission for mental illness in patients with severe unipolar depression". Notably, outcomes associated with the most widely used treatments (antidepressants, aripiprazole, and quetiapine) are modest compared with outcomes associated with lithium. Replication of these findings is needed, and should be possible given that similar databases exist in

other countries (eg, Denmark and Taiwan). These data could be easily assessed to establish whether they replicate the Finnish findings or not. The findings of Tiihonen and colleagues are particularly noteworthy because of recent disquiet about the use of antidepressants in unipolar mood disorders,<sup>9</sup> and they suggest that lithium monotherapy might be the best long-term prophylactic drug.

The findings of Tiihonen and colleagues might also reawaken research interest in lithium, which has waned in recent decades. Lithium is not simply a medicine, but an element present in the natural environment and in both food and drinking water to varying degrees. Of the many potential effects of environmental lithium on brain and behaviour, a reduction in suicide prevalence at a population level is the most consistently found, an effect that appears to be independent of lithium prescriptions.<sup>10</sup> The findings of Tiihonen and colleagues from their Finnish National data should be replicated; more randomised trials of lithium monotherapy in unipolar depression should be conducted and, if the benefits are verified, practice should reflect this. Finally, all aspects of lithium and its effects on the brain and behaviour should be the focus of continuing rigorous scientific enquiry.

Allan H Young

Centre for Affective Disorders, Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8AZ, UK

allan.young@kcl.ac.uk

Prof Young is employed by King's College London as an Honorary Consultant SLaM (NHS UK), and has been paid for lectures and advisory boards for the following companies with drugs used in affective and related disorders: AstraZeneca, Eli Lilly, Janssen, Lundbeck, Sunovion, Servier, Livanova. This report represents independent research funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author and not necessarily those of the NHS, the NIHR, or the Department of Health.

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